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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/670,122	09/24/2003	Salim Yusuf	16554-002001	2547

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EXAMINER	
VENCI, DAVID J	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 02/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/670,122	YUSUF ET AL.	
	Examiner	Art Unit	
	David J Venci	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *November 19, 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-9,14,16 and 18-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-9, 14, 16 and 18-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment filed November 19, 2004, which cancelled claims 2-3, 10-13, 15 and 17, added new claims 18-24, and amended claims 1, 4, 6-7, 9, 14 and 16 is acknowledged.

Currently, claims 1, 4-9, 14, 16 and 18-24 are pending before the Office.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

Claims 1, 4-9, 14, 16 and 18-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1 and 4, the claim preambles do not correspond to the method outcomes. For example, the preambles recite "a method for assessing aspirin resistance" or "a method for assessing relative risk of a cardiovascular event in a patient taking aspirin." Both claims recite the step of comparing the concentration of metabolite to a predetermined set of concentration quartiles comprising a first quartile, a second quartile, a third quartile and a fourth quartile; and determining within which quartile the sample concentration falls wherein a concentration of the metabolite or relative risk within the second, third or fourth quartile is indicative of aspirin resistance and resistance increases with each increasing quartile. However, it is not clear how merely comparing the concentration of metabolite to a predetermined set of concentration quartiles amounts to a method for assessing aspirin resistance, or a method for assessing relative risk of a cardiovascular event in a patient taking aspirin, absent baseline or numerical values for comparision.

Claims 1 and 4 are rejected further under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are the steps of determining, or defining, a set of concentration quartiles. It is not clear how it is possible to compare metabolite concentrations to a "predetermined set of concentration quartiles" when the "predetermined set of concentration quartiles" is not defined.

Claims 14, 16, 19 and 21-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the claims do not enable a person skilled in the art to use a method wherein "a concentration of thromboxane B2 at less than 15.1 ng/mmol creatinine corresponds to a first quartile value, a concentration of thromboxane B2 at 15.1 to 21.8 ng/mmol creatinine corresponds to a second quartile value, a concentration of thromboxane B2 at 21.9 to 33.7 ng/mmol creatinine corresponds to a third quartile value, and a concentration of thromboxane B2 at equal to or greater than 33.8 ng/mmol creatinine corresponds to a fourth quartile value; determinine which quartile the sample concentration falls within and determining the relative risk based on the quartile value of the sample compared to a first quartile value."

The specification teaches a table (see Table 3) that appears to summarize data derived from statistical analysis performed on data obtained from the HOPE study, which studied the effects of ramipril and vitamin E for the secondary prevention of cardiovascular disease (see para. [0068]). Table 3 describes the relationship between 11-dehydro thromboxane B2 concentrations with the odds ratio of myocardial infarction, stroke, and cardiovascular death (hereinafter "MI/Stroke/CV death"). · The specification also teaches several methods for determining 11-dehydro thromboxane B2 concentrations (see e.g. para. [0047]).

The specification does not appear to teach a correlation between 11-dehydro thromboxane B2 concentrations with aspirin resistance or risk of a cardiovascular event. Indeed, in the data presented in Table 3, for which Applicants' claimed invention relies upon, there is a high degree of overlap in the 95 % confidence intervals between the four quartiles. For example, there is almost complete overlap in the 95 % confidence intervals for MI/Stroke/CV death odds ratio between the 15.1-21.8 quartile and the 21.9-33.7 quartile. In addition, the P values for the trend appear to be less than the significance level of α = 0.05. Therefore, a person of ordinary skill would conclude that there is sufficient evidence to warrant rejection of the proposition that there is a correlation between aspirin resistance and 11-dehydro thromboxane B2 concentrations in the given concentration range, or that there is a correlation between the risk of a cardiovascular event in a patient taking aspirin and 11-dehydro thromboxane B2 concentrations in the given concentration range.

According to Strongin (1993, "Sensitivity, Specificity and Predictive Value of Diagnostic Tests: Definitions and Clinical Applications", in Laboratory Diagnosis of Viral Infections, Lennette, e., ed., Marcel Dekker, Inc., New York, pp. 211-219) a number of characteristics need to be considered in the development of any suitable diagnostic assay. These characteristics include the following: (1) the sensitivity of the assay; (2) the true-positive test rate; (3) the false-negative test rate; (4) the specificity, or percentage of patients without the disease who will display a negative result; (5) the true-negative test rate; (6) the false-positive test rate; (7) the predictive value, or the probability that the test result is correctly indicating the presence or absence of the disease; (8) the prevalence, or number of patients in any given population that have the disease in question; (9) the efficiency or percentage of all results that are true; (10) the accuracy of the recited diagnostic assay.

Additional considerations must also be examined to enable the clinician to practice the invention, including assessment of the following: (1) when is the maximum sensitivity desired? (2) when is the maximum specificity desired?; (3) when is the maximum efficiency desired?; (4) How is the maximum sensitivity or specificity achieved?; (5) how is the predictive value maximized? An essential understanding

of these factors is required to enable the skilled artisan to accurately use and interpret any given diagnostic test.

Because of the lack of description in the specification for the claimed method, the data presented in Table 3 and the examples do not allow the conclusive determination that anyone or everyone who has a certain level of 11-dehydro thromboxane B2 has a certain propensity for aspirin resistance. Since the specification lacks any teaching of a method for correlating 11-dehydro thromboxane B2 concentrations with aspirin resistance, or whether any considerations were given to any of the characteristics state above, it would require undue experimentation for one skilled in the art to make and use the invention as claimed.

Claim Rejections - 35 USC § 103

Claims 1, 4-9, 14, 16 and 18-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ens (WO 01/31052) in view of Cipollone et al., 102 CIRCULATION 1007 (2000) and Encyclopedia of Biostatistics, Armitage & Colton, Eds. (1998) (hereinafter "Armitage & Colton").

Ens describes a method for assessing aspirin resistance (See Example 2, p. 10, line 23) in a patient by measuring a thromboxane A2 metabolite (See Example 2, p. 10, line 19, "11-dehydro TXB_2") in a sample of body fluid (See Example 2, p. 10, line 19, "Urine"), assessing risk of a cardiovascular event (See Example 2, p. 11, line 19, "potential thrombotic events") in a patient taking aspirin (See Example 2, p. 11, line 17, "aspirin users"). In addition, Ens describes the division of data into 11 different concentration quantiles (see Table 2).

Ens does not teach a method comprising the step of creating a predetermined set of concentration quartiles. Ens does not teach a method wherein "a concentration of thromboxane B2 at less than 15.1 ng/mmol creatinine corresponds to a first quartile value, a concentration of thromboxane B2 at 15.1 to 21.8 ng/mmol creatinine corresponds to a second quartile value, a concentration of thromboxane B2 at

21.9 to 33.7 ng/mmol creatinine corresponds to a third quartile value, and a concentration of thromboxane B2 at equal to or greater than 33.8 ng/mmol creatinine corresponds to a fourth quartile value; determinine which quartile the sample concentration falls within and determining the relative risk based on the quartile value of the sample compared to a first quartile value."

However, Armitage & Colton teach the use of quantiles, including division into quartiles, as a useful tool for modeling risk relationships (See pp 3628-9). In addition, Armitage & Colton teach the use of nested case-contol studies to determine risks through the estimation of odds ratios from logistic regression (See p. 17, col. 1, Estimation from Population-Based or Nested Case-Control Studies, first paragraph). Cipollone et al. teach a similar range (17.0–28.3 ng/mmol) of 11-dehydro-TXB_2 concentrations in patients taking aspirin (See p. 1010, Fig. 6(right), estimating 11-dehydro-TXB_2 concentration range is approximately 150 - 250 pg/mg in patients taking aspirin, and assuming creatinine MW = 113.12 g/mol).

Therefore, it would have been obvious for a person of ordinary skill in the art to combine the method for assessing aspirin resistance and risk of cardiovascular event, as taught by Ens, with the use of quartiles to express the 11-dehydro-TXB_2 concentration range of Cipollone et al. because Armitage & Colton teach that the use of quantiles is useful for modeling risk relationships, while "Cipollone teaches a normal range of 17.0-28.3 ng/mmol of 11-dehydro-thromboxane B2 in patients taking aspirin" (see Applicants' response at p. 11, fourth paragraph).

With respect to claim 5, Ens describes a method wherein a patient has arterial vascular disease (See Summary of the Invention, p. 7, lines 24-26, "The present invention... provides a method for identifying... aspirin dose for a patient...") (See also Background of the Invention, p. 3, lines 10-12, "Aspirin is indicated for patients with stable angina, unstable angina, acute myocardial infarction, transient cerebral ischemia, thrombotic stroke, and peripheral arterial disease") (emphasis added).

With respect to claims 6-7, Ens describes a method wherein ELISA (See Example 2, p. 10, line 29, "acetylcholinesterase-linked enzyme immunoassay") is used to determine the concentration of thromboxane-A2 metabolite.

With respect to claim 8, Ens describes a method using urine (See Example 2, p. 10, line 19, "Urine").

With respect to claims 9 and 18, Ens describes a method wherein 11-dehydro-TXB_2 is measured (See Example 2, p. 10, line 19, "11-dehydro TXB_2").

Response to Arguments

In prior Office Action, claims 1, 4-9 and 17 were rejected under 35 USC 102(b) as being anticipated by Ens (WO 01/31052). Applicants have amended claims 1 and 4 to include the limitation of "comparing the concentration of the metabolite in the sample to a predetermined set of concentration quartiles comprising a first quartile, a second quartile, a third quartile and a fourth quartile; and determining within which quartile the sample concentration falls" wherein a concentration of the metabolite or relative risk within the second, third or fourth quartile is indicative of aspirin resistance and resistance increases with each increasing quartile. Applicants argue that "nowhere in Ens is it taught or suggested using a predetermined set of concentration quartiles to determine aspirin resistance" (see Applicants' Remarks at p. 10, fifth paragraph). This rejection is withdrawn in light of Applicants' amendement to the claims, and in light of new rejection under 35 U.S.C. 103(a) as being unpatentable over Ens in view of Cipollone et al. and Armitage & Colton, set forth supra.

In prior Office Action, claims 2-3 and 10-16 were rejected under 35 USC 103(a) as being unpatentable over Ens (WO 01/31052) in view of Cipollone et al., 102 CIRCULATION 1007 (2000) and Encyclopedia of Biostatistics, Armitage & Colton, Eds. (1998) (hereinafter "Armitage & Colton"). Applicants have amended claim 14 to include the limitation wherein "a concentration of thromboxane B2 at less than 15.1 ng/mmol creatinine corresponds to a first quartile value, a concentration of thromboxane B2 at 15.1 to 21.8

ng/mmol creatinine corresponds to a second quartile value, a concentration of thromboxane B2 at 21.9 to 33.7 ng/mmol creatinine corresponds to a third quartile value, and a concentration of thromboxane B2 at equal to or greater than 33.8 ng/mmol creatinine corresponds to a fourth quartile value; determinine which quartile the sample concentration falls within and determining the relative risk based on the quartile value of the sample compared to a first quartile value." Applicants argue that "as none of Ens, Cipollone, and Armitage suggests the concentration range of 11-dehydro-thromboxane B2 relative to creatinine in each quartile as recited in claim 14, a combination of these references fails to do so" (see Applicants' Remarks at p. 11, fourth paragraph). Applicants' argument has been carefully considered but is not persuasive because one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Armitage & Colton teach that the use of quantiles is useful for modeling risk relationships, while "Cipollone teaches a normal range of 17.0-28.3 ng/mmol of 11-dehydro-thromboxane B2 in patients taking aspirin" (see Applicants' response at p. 11, fourth paragraph).

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the

advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J Venci whose telephone number is 571-272-2879. The examiner can normally be reached on 08:00 - 16:30 (EST). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David J Venci
Examiner
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02/05/05